REMARKS

Claims 11 and 19 are amended herein to recite administration of the compound of formula (I) "to a subject not having benign prostatic hyperplasia or symptomatic prostatism". Support is found, for example, at paragraph [0023] of the specification. In this connection, Applicants note that alternative embodiments recited in the specification may be explicitly excluded in the claims. See, e.g., MPEP § 2173.05(i).

No new matter is presented.

Further to the Response filed January 5, 2010, Applicants submit that the presently claimed invention is patentable over the cited references for the reasons of record and in view of the claim amendments.

Claims 11-14, 17, and 19 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tanaka et al. (WO 00/02846) (hereinafter "Tanaka") in view of Broten et al. (U.S. Patent No. 6,410,554) (hereinafter "Broten") in light of the Mesh Supplementary Data (2009). Applicants respectfully traverse on the basis that the references do not teach or suggest anything about the effect of KMD-3213 (silodisin) on the frequency or urinary incontinence in a patient not having benign hyperplasia or symptomatic prostatism.

More specifically, (1) the teachings of Tanaka and Broten do not provide a reason to a person having ordinary skill in the art to use silodosin alone or in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence in a subject not having benign prostatic hyperplasia or symptomatic prostatism as recited in the present claims; and (2) the unexpected results obtained by the

presently claimed invention rebut any *prima facie* case of obviousness that may have been set forth.

(1) The teachings of Tanaka and Broten do not provide a reason to a person having ordinary skill in the art to use silodosin alone or in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence in a subject not having benign prostatic hyperplasia or symptomatic prostatism. As the Office Action has admitted, Broten only teaches the administration of KMD-3213 (actually, in combination with an endothelin antagonist - not alone) for the treatment of lower urinary tract symptoms including increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia (see column 6). In this connection, Broten specifically teaches that an α1-a antagonist will inhibit the intrauretheral pressure response to phenylephrine (see Example 14). However, Broten does not teach or suggest the effect of KMD-3213 on frequency or urinary incontinence in patients not having benign prostates hyperplasia or symptomatic prostatism.

As Broten also teaches, α1-adrenoceptor antagonists may inhibit prostatic urethral contraction (see column 30, Example 14). On the other hand, α1-adrenoceptor agonists induce contraction of the urethra. Nishimatsu et al. (see the Abstract of the attached reference) teach that an α1-adrenoceptor agonist (NS-49) is considered useful for the treatment of urinary stress incontinence due to the effect of contraction of the human urethra. Therefore, one of ordinary skill in the art would not expect that silodosin, an α1A-adrenoceptor antagonist having the opposite activity, would be effective for the treatment of urinary incontinence.

In addition, as previously pointed out, for the treatment of frequency or urinary incontinence, anticholinergics, antispasmodics, and the like have been used (see the attached portion of American Family Physician, 2006, Vol. 74(12), 2061-2068), and β3 adrenoceptor agonists are developed (see, for example, Tanaka, column 2, lines 34-41 and column 3, lines 13-18). These drugs mainly target smooth muscle of the bladder (see American Family Physician, at p. 2061, left column, lines 1-6 and the paragraph entitled "Pathophysiology" at p. 2061, right column to p. 2063, left column, line 7, previously submitted with the Response filed January 5, 2010). As of the filing date of the present application, however, there was no report showing that silodosin has an inhibitory activity against contraction of the bladder, whereas silodosin was known to suppress uretheral contraction and be useful as an agent for the treatment of dysuria (column 9, lines 37 and U.S. Patent No. 5,387,603 at column 1, lines 7-14). "Dysuria" means difficulty or pain in urination (see the definition from Stedman's Medical Dictionary previously submitted with the Response filed January 5, 2010). Therefore, a person having ordinary skill in the art would not have expected (with any reasonable expectation of success) that silodosin would be effective for the treatment of frequency or urinary incontinence which is unrelated to benign prostatic hyperplasia or symptomatic prostatism based on the disclosure of the cited references.

Furthermore, in the micturition interval measurement as shown in Example 2 of the present specification, the inventors used the acetic acid-stimulated frequency model, which is a frequency model independent of the presence or absence of urinary obstruction. Therefore, the

results on silodosin show the direct effect improving urinary frequency of silodosin, not a secondary effect by inhibiting contraction of urethra.

Accordingly, Applicants respectfully submit that the teachings of Tanaka and Broten do not provide a reason to a person having ordinary skill in the art to use silodosin alone or in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence in a subject not having benign prostatic hyperplasis or symptomatic prostatism.

(2) The unexpected results obtained by the presently claimed invention rebut any *prima facie* case of obviousness that may have been set forth. Although Applicants submit that, for at least the reasons set forth above, the Office Action failed to set forth a *prima facie* case of obviousness, Applicants respectfully submit that the unexpectedly superior results demonstrated in the present specification rebut any such showing.

Applicants first respectfully disagree with the position set forth in the Office Action that "in order for superadditive or superior results to be concluded, each agent must be administered at the same dosage and then the combination of the two agents compared to the change of micturition interval demonstrated by each individual agent." It is unclear what authority the Office is citing for such a position, and Applicants respectfully submit that such a position is incorrect.

As shown in Example 2 and Figure 2 of the present specification, the changes in the micturition intervals were 99.5%, 115.2%, 116.3% and 163.8% in the control group, the silodosin administration group, the compound 2 administration group, and the combination

group thereof, respectively. The differences of the change in micturition interval from control group are also shown in the following table.

Group	Control group	Silodosin group	Compound 2 group	Combination group
Dosage of Silodosin (mg/kg)	0	0.03	0	0.03
Dosage of Compound 2 (mg/kg)	0	0	1	1
Change in micturition interval	99.5	115.2	116.3	163.8
Difference from control group (%)	-	+15.7	+16.8	+64.3

The table illustrates that in the silodosin group, the micturition interval increased by 15.7% more than that in the control group, and in the Compound 2 group, it increased by 16.8% more than that in the control group. If the combination administration of silodosin and Compound 2 were to give only additive results, it would be expected to increase by only 32.5% (15.7% plus 16.8%) more than the control group. Unexpectedly, however, the combination administration exerted 64.3% more than control group, which is almost two times higher than expected.

Furthermore, it was also confirmed that the combined administration of silodosin and compound 2 exhibited a synergistic effect by a statistical method as well (see Paragraph No. [0030] of the present specification).

Accordingly, although Applicants disagree that the Office Action set forth a *prima facie* case of obviousness, Applicants respectfully submit that the unexpected results obtained by the

presently claimed invention rebut any *prima facie* case of obviousness that may have been set forth.

Accordingly, Applicants respectfully request withdrawal of the rejection.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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